The essential inquiry for determining indefiniteness is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness must be analyzed in light of the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. (M.P.E.P. 2173.02) One of skill in the art would certainly understand that the phrase "fermented hyaluronan" means hyaluronan produced by the process of fermentation. One of skill in the art would further understand that the process of fermentation refers to a process in which organic substances are broken down by microorganisms to yield incompletely oxidized products. (See, for example, The Dictionary of Cell and Molecular Biology Online at www.mblab.gla.ac.uk/~julian/dict2.cgi?2336.) The process of fermentation differs markedly from processes whereby hyaluronan is isolated from natural sources, such as rooster comb or umbilical cords. In light of this straightforward definition of fermentation, the Examiner's confusion is difficult to understand. The Examiner's statement that "it is unclear if hyaluronan (HYN) is a product of any non-warm-blooded vertebrate, or if fermented HYN is a product produced by streptococcal fermentation of HYN, or if it is derived by other means" suggests that one of skill in the art would be unclear as to both the source of the hyaluronan and the means by which it is obtained. This is simply not true. Both the source of the hyaluronan, i.e. microorganisms, and the means by which the hyaluronan is produced, i.e. fermentation, would be clear to one of skill in the art based on the phrase "fermented hyaluronan." With regard to whether the hyaluronan is limited to hyaluronan produced by Streptococcal fermentation, the specification clearly states that the hyaluronan may be obtained by any process well known in the art and that the fermentation of Streptococcus is merely one such process.

For the reasons outlined above, applicants respectfully request that the rejection be withdrawn.

The Examiner rejected claim 6 under 35 U.S.C. § 112, second paragraph, due to insufficient antecedent basis for the phrase,"the citrate" in claim 1, the claim from which claim 6 depends. Claim 6 has been amended to depend from claim 2. Applicants believe that this amendment renders the claim definite and request that the rejection be withdrawn.

Finally, claim 31 was rejected under 35 U.S.C. § 112, second paragraph, due to insufficient antecedent basis for the phrase, "the media that can support embryo or cell development" in claim 30, the claim from which claim 31 depends. Claim 30 has been amended

to clarify that the medium can support mammalian embryo and cell development. Applicants believe that this amendment renders the claim definite and request that the rejection be withdrawn.

II. Rejection of Claims Under 35 U.S.C. § 102

In the Office Action, the Examiner rejected claims 17 and 19 under 35 U.S.C. § 102(b) as being anticipated by Miyano, *et al.* The Examiner also rejected claims 1, 2, 7-13, and 18 under 35 U.S.C. § 102(e) as being anticipated by United States patent number 6,140,121, issued to Ellington, *et al* (hereinafter "Ellington"). In making this rejection the Examiner noted that "without any evidence disclosed in the specification that the fermented hyaluronan and hyaluronan are structurally different, it is concluded that fermented hyaluronan and hyaluronan are structurally identical. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." In rejecting claims 1, 2, 7-13, 17, and 18, the Examiner further stated, "there is no evidence disclosed in the specification that recombinant human albumin and human albumin are structurally different. . . . Therefore, recombinant human albumin and human albumin are functionally identical based on their identical chemical structures." Applicants respectfully traverse.

In order to establish a prima facie case of obviousness the Examiner must show that the cited reference teaches each and every limitation of the claims. Here, the Examiner has admitted that neither Miyano, *et al.* nor Ellington teaches a culture medium containing *fermented* hyaluronan. The Examiner further admits that Ellington does not teach the use of recombinant human albumin. The Examiner tries to circumvent these important distinctions by asserting that fermented hyaluronan and hyaluronan isolated from natural sources have identical chemical compositions and further that recombinant human albumin and human serum albumin isolated from blood products have identical chemical compositions. This is not true.

The differences between fermented hyaluronan and hyaluronan isolated from natural sources is explained in the specification at page 3, paragraph 9, which states, "the use of fermented HYN has several advantages over the use of HYN from a naturally occurring warm blooded vertebrate source such as purified from rooster comb or umbilical cord," including the ability to control the safety and stability of the hyaluronan. The difference between the

fermented and isolated product is also discussed in Kjeins, *et al.*, Isolation of Hyaluronic Acid From Cultures of Streptococci in a Chemically Defined Medium, Acta Path. Microbiol. Scand. Sect. B, 84, 162-164, (1976) which is incorporated into the pending application by reference. Specifically, table 2 of that article shows that hyaluronan produced by fermentation has significantly fewer protein contaminants than hyaluronan isolated from umbilical cord. On page 164, the article explains the importance of this difference stating, "The use of a chemically defined medium for the preparation of hyaluronic acid ensures reproducibility in the yield and degree of purity of the hyaluronic acid. Complications associated with the fact that an undefined substrate contains substances of high molecular weight, e.g. protein, are avoided." A copy of this reference is enclosed for your convenience.

The differences between recombinant human albumin and human albumin isolated from blood products are discussed throughout the pending application. For example, on page 1, paragraph 2, the specification points out that one drawback to the use on human albumin derived from human blood serum is the possibility of contaminants, including impurities, toxins, and infective agents found in the fluid from which the human albumin is derived. In addition, on page 8, paragraph 24, the specification states "an advantage of the supplement of the present invention is that it eliminates the potential contamination associated with the use of blood products in media for culturing embryo and other mammalian cellular materials."

As amply demonstrated by the preceding discussion, fermented hyaluronan and recombinant human albumin are purer, safer, and more chemically reproducible than their naturally isolated counterparts. Thus, the Examiner's contention that the properties of fermented hyaluronan and recombinant human albumin are necessarily present in the prior art is false. Because the Examiner relied on this false assumption in making the pending rejections, the rejections should be withdrawn.

III. Rejection of Claims Under 35 U.S.C. § 103

In the Office Action the Examiner rejected claims 1-5, 10-20, 30, 32, and 33 under 35 U.S.C. § 103 as being unpatentable over United States patent number 6,153,582 issued to Skelnick (hereinafter "Skelnick") in view of United States patent number 5,612,196 issued to Becquart (hereinafter "Becquart"). The Examiner also rejected claims 1-5, 10-20, 26-30, 32 and 33 as unpatentable over Skelnick in view of Becquart and further in view of the Strategene Catalog of 1998. The Examiner notes that Skelnick discloses a serum-free composition for

culturing human corneal cells comprising hyaluronic acid, albumin, and sodium citrate. The Examiner further notes that Becquart teaches a recombinant human albumin having all the properties of human albumin extracted from sera. In support of the rejections, the Examiner states, "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the media of Skelnick by substituting the recombinant human albumin taught by Becquart. The motivation to do so would have been to make a serum-free media free of non-human serum (such as albumin, a serum protein) as suggested by Skelnick and to reduce the probability of inducing an immune response . . . as suggested by Skelnick and Becquart." Applicants respectfully traverse these rejections.

In order to establish a prima facie case of obviousness, the Examiner must show that the cited references, alone or in combination, teach each and every limitation of the rejected claims. The Examiner has failed to meet this burden for at least two reasons. First, none of the cited references teach a culture medium containing *fermented* hyaluronan, as required by rejected claims 1-5, 12, 13, 17-20, 26-30, 32, and 33. Thus, for the reasons discussed above, the cited references fail to teach each and every claim limitation and the rejection should be withdrawn. Second, even if the cited references had taught the use of fermented hyaluronan, there is nothing in the teaching of the references to suggest that substituting the recombinant human albumin of Becquart for the human albumin of Skelnick would produce a mammalian culture medium or a culture medium supplement that is capable of increasing the viability of gametes or embryonic cells as recited in claims 1, 10, 17, 21, 24, 26, 30, and 33. As amended, each of the independent claims in the present application recite a mammalian culture medium or a culture medium supplement that is capable of increasing the viability of gametes and embryos. In contrast, Skelnick is directed to a medium for the preservation of corneal tissue. The medium taught by Skelnick is a complex mixture of at least sixteen different ingredients. The Examiner points to no evidence that the medium of Skelnick would be suitable as a gamete or embryo culture medium. Therefore, applicants respectfully request that the rejection be withdrawn.

Finally, with respect the claims 30 and 33, applicants drawn the Examiner's attention to the transitional phrase "consisting essentially of." This partially closed claim language limits the claims to compositions containing the elements specifically listed therein and other ingredients that do not interfere with or contribute to the activity of the composition. As noted in the discussion above, the corneal tissue preserving solution taught by Skelnick contains

at least sixteen different ingredient, each of which contributes to the activity of the medium. Therefore, Skelnick does not render claims 30 and 33 unpatentable, and the rejection should be withdrawn.

IV. Conclusion

In view of the foregoing remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejections discussed above. If Examiner Angell has any questions, or believes a telephone discussion would expedite prosecution, he is invited to contact the undersigned.

Respectfully Submitted

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CLAIM AMENDMENTS

6. (Once Amended) The supplement according to claim [1]2, wherein the citrate is present in a range of about 0.1 mM to about 1.0 mM when added to the medium.

10. (Once Amended) A mammalian culture medium comprising recombinant human albumin and a medium that can support cell development, wherein the mammalian culture medium is capable of increasing the viability of gametes or embryonic cells cultured in the medium.

17. (Once Amended) A mammalian culture medium comprising fermented hyaluronan and a medium that can support cell development, wherein the mammalian culture medium is capable of increasing the viability of gametes or embryonic cells cultured in the medium.

26. (Once Amended) A kit for supplementation of mammalian culture medium, comprising:

(a) a medium comprising one or more ingredients selected from the group consisting of mammalian culture medium, recombinant human albumin, fermented hyaluronan, citrate and combinations thereof, wherein the medium is capable of increasing the viability of gametes or embryonic cells cultured in the medium; and

(b) instructions for use of the kit.

30. (Once Amended) A mammalian culture medium consisting essentially of:

(a) a medium that can support mammalian embryo or cell development;

(b) recombinant human albumin in an amount from about 0.1 mg/ml to about 20.0 mg/ml;

(c) fermented hyaluronan in an amount from about 0.1 mg/ml to about 5.0 mg/ml; and

(d) citrate in a concentration from about 0.1 mM to about 5.0 mM,

wherein the mammalian culture medium is capable of increasing the viability of gametes or embryonic cells cultured in the medium.

33. (Once Amended) A mammalian culture medium supplement consisting essentially of:

(a) recombinant human albumin in an amount from about 0.125 mg/ml to about 20.0 mg/ml;

(b) fermented hyaluronan in an amount from about 0.1 mg/ml to about 5.0 mg/ml; and

(c) citrate in a concentration from about 0.1 mM to about 5.0 mM,

wherein the mammalian culture medium is capable of increasing the viability of gametes or embryonic cells cultured in the medium.